Expressions follow SCOTUS gene ruling

Elizabeth Silverman

July 2013—The U.S. Supreme Court last month handed down a landmark decision on a narrow issue with broad implications for molecular medicine: Can genes be patented? In ruling that as products of nature, genes did not meet the criteria for patent eligibility, the Court brought its collective wisdom to bear on an issue that has troubled physicians, ethicists, and patients for nearly 20 years and hindered innovators in academia and industry. The Court declared invalid the patents on the genes *BRCA1* and *BRCA2*, patents that were at the heart of an intellectual property estate that enabled Myriad Genetics to create a commercial monopoly in *BRCA* testing.

For all its apparent clarity, the full implications of the Court's decision on *BRCA1* and *BRCA2* testing, and on products outside of genetic diagnostics, will probably not be known for some time. Also uncertain are Myriad's intentions. Whether the company can or will use any of its remaining intellectual property to continue to try to block others from *BRCA* testing is an open question, particularly in light of its historically aggressive stand on patent enforcement. For now, those interested in offering genetic tests believe the Supreme Court's decision has given them a powerful legal tool to do so, in *BRCA1* and *2* testing and beyond. "The ruling gives pathologists freedom to operate in the genome," says Debra Leonard, MD, PhD, professor and chair, Department of Pathology, University of Vermont College of Medicine and Fletcher Allen Health Care.

Dr. Leonard

In the immediate aftermath of the Court's decision, academic institutions such as the University of Washington and Montefiore Medical Center announced they would be offering *BRCA1* and *2* testing. Commercial laboratories Ambry Genetics, GeneDx, Quest, DNA Traits, and Pathway Genomics followed suit. Ambry Genetics launched its test the day of the ruling and, says Ambry's chief medical officer, Elizabeth Chao, MD, two independent legal teams concluded Ambry did have the freedom to operate. Ambry received four samples the day after it launched the test.

Although the Court's decision was made on the narrow question of gene patents, the effects of its decision are expected to be far-reaching. Physicians will now have the same freedom of choice in diagnostic testing that has historically been the case with other diagnostic analytes, where patenting is an anomaly. Pathologists and lab directors are now free to bring testing in-house after evaluating technical proficiency, test volumes, and availability of specialized patient counseling. One who will undertake such analysis is Gregory Tsongalis, PhD, professor of pathology and director of molecular pathology, Dartmouth-Hitchcock Medical Center, who cautions: "These are complex tests and require careful counseling, and it may not be right for many labs to jump into it."

Pathologists will also now be able to compare a number of outside commercial laboratories on quality, cost, time to result, and technology to make choices that are in the best interests of patients.

One thing they will not be doing: spending time huddled with legal teams trying to untangle what they can and cannot do in their laboratories. Margaret Gulley, MD, professor in the Department of Pathology and Laboratory Medicine, University of North Carolina, speaking in a CAP webinar in June after the Court decision, said: "Until last week a major consideration in whether to bring on a new test was not how much it would benefit our patients, but whether we would be likely to face a lawsuit for gene patent infringement. This decision opens the door for us to put patient needs first."

Other effects of the ruling are wider access to second opinion testing and lower-cost tests. “Although mistakes are uncommon, some patients may still want a second opinion if they are considering surgery to make sure they are getting a correct result,” says Roger D. Klein, MD, JD, pathologist in the Department of Molecular Pathology, Cleveland Clinic. Arthur Caplan, PhD, professor and head of the Division of Bioethics at NYU Langone Medical Center, calling the Court’s ruling “correct,” says, “It will open up competition and enable second opinion tests.” Moreover, as long as Myriad remained the sole provider of tests with limited recourse to second opinions, there was no systematic way to evaluate the quality of its results. This situation is expected to change with the introduction in time of CAP proficiency tests. In fact, with respect to many aspects of *BRCA1* and *2* testing—analyte patentability, freedom to offer in-house testing, ability to evaluate outside laboratories on measurable performance metrics, availability of second opinion testing, and ultimately proficiency testing—the Supreme Court decision appears to have normalized an aberrant situation in medical diagnostics and enabled it to be brought into line with current clinical standards.

Dr. Klein

Myriad currently charges $3,000 to $4,000 for its *BRCAnalysis* test—strikingly high compared with the dramatic decrease in the cost of gene sequencing over the past decade. For some women, the cost of *BRCA* testing created a barrier to care. The Supreme Court ruling “is a major step forward in providing patients with opportunities to have genetic tests done cheaper and available in panels of genes,” says Banu Arun, MD, professor of breast medical oncology and clinical cancer prevention, and co-director of clinical cancer genetics, The University of Texas MD Anderson Cancer Center.

Although many insurance carriers cover the cost of *BRCA* testing, “about 10 percent of our patients who need the test are uninsured,” Dr. Gulley says of the UNC. In addition, there are women whose insurance plans do not cover the test or for whom copays are prohibitive. Ambry quickly committed to a $2,200 price tag while DNA Traits announced testing for $995. Harry Ostrer, MD, professor of pathology, genetics, and pediatrics at Albert Einstein College of Medicine, says costs will come down because payers will pressure all labs. “Payment will be dictated by the new CPT codes that were implemented in January. Out-of-pocket expenses will be less for patients,” he says.

Mary-Claire King, PhD, professor of genome sciences and medicine at the University of Washington and discoverer of the *BRCA1* gene, says, “There’s no question that not having testing available for all breast and ovarian cancer genes has cost lives. It’s an enormous relief that there will now be an open marketplace where a variety of approaches can be used.”

Myriad’s patents restricted use of the *BRCA1* and *2* genes in new panels of breast and ovarian cancer susceptibility genes. Although the *BRCA1* and *2* genes are the most prevalent of the breast and ovarian cancer susceptibility genes and account for five to 10 percent of all breast and ovarian cancers, they are not the only ones of clinical interest. These multigene susceptibility panels use next-generation sequencing and run on efficient, cost-effective DNA sequencers that read full-length genomic DNA. This makes them ideally suited to read large panels of genes. Myriad, by contrast, uses the Sanger method to test for mutations only in the *BRCA* genes. Next-gen sequencing “will allow the detection of all classes of mutations in *BRCA1, BRCA2,* and multiple other genes that similarly harbor inherited mutations that lead to very increased risks of breast cancer or ovarian cancer or both,” Dr. King said in the CAP webinar. These tests have been available in the research sphere since 2010, she added, but were not available to patients clinically until the Court ruled in June. The Cleveland Clinic’s Dr. Klein sounds a note of caution on susceptibility panels because counseling models are currently single-gene-based and “The more you look for, the more you find. Variants can be misclassified,” he notes. “There will have to be some refinement in

them." He encourages that such testing take place as part of clinical studies whenever possible.

One of the larger issues looming in the wake of the ruling is the adequacy of publicly available databases of *BRCA1* and *2* variants for interpreting test results. While most of the sequence variants that represent either harmless, normal variation or susceptibility-enhancing mutations are known, there are other variants whose significance is unknown. Myriad has the largest database of these variants of unknown significance (VUS) based on the 1 million patients whose *BRCA1* and *2* genes it has analyzed, information it stopped sharing via public databases in late 2004. Therefore, any testing done outside of Myriad, academic or commercial, will need to rely on publicly available information, such as that contained in the National Center for Biotechnology Information's ClinVar database and the Leiden Open Source Variation Database. Robert Nussbaum, MD, chief of medical genetics at the University of California, San Francisco, has also been collecting variants for a publicly available database.

Because *BRCA1* and *2* variants of uncertain clinical significance are found in a minority of patients, and most cancer-causing mutations are relatively straightforward to recognize or already known—only three account for the vast majority of mutations in women of Ashkenazi Jewish descent, for instance—Dr. Klein believes questions will arise in a limited proportion of patients. "Although Myriad has a competitive marketing advantage because of its internal database, the advantage will diminish over time as more variants are added to the public database." Dr. King believes "physicians are in a good position to advise their patients using the public database." And Dr. Arun of MD Anderson says, "Although clinical interpretation would be easier if physicians could get the data from Myriad, tests in Europe are being done using the publicly available database."

Nevertheless, Robert Cook-Deegan, MD, research professor of genome ethics, law, and policy at Duke University, writing in the June 21 *European Journal of Human Genetics*, says Myriad's claim of a rate of three percent VUS contrasts with the 20 percent rate reported by European testing services and the discrepancy is due at least in part to the information Myriad possesses but does not share. Dr. Nussbaum believes the rate of publicly available VUS is closer to 10 percent, and says: "We are in a transition period. For six months or so there may be a difference in the rate of VUS in Myriad's database compared to what's out in the public database. But there is a tremendous amount of genome sequencing going on so we are getting a much better picture of what is normal in a *BRCA* gene. Right now we don't have a full picture of normal variation, but it is getting filled in quickly by all of the sequencing being done."

Now that *BRCA1* and *2* testing has been freed from legal restrictions, the database issues are expected to be short term because more information can be gathered from more sources, both academic and commercial. "We must now move forward to put into the public domain much of the information held by individual providers," says the University of Vermont's Dr. Leonard. Dr. Gulley of UNC agrees: "We need better databases to help us interpret genetic test results. Pathologists need variant databases not just for cancer genes but all genes we test for, including microbial genes and so forth." Over time, publicly available information is expected to surpass that held by Myriad, particularly because other commercial labs are interested in working with the pathology community.

The publicity surrounding the Court's decision and the media attention paid to Angelina Jolie's prophylactic mastectomy have raised important issues. The test is performed now on a select group of women whose family history and ethnicity place them at high risk for breast and ovarian cancer. However, the wider availability of more affordable *BRCA1* and *2* tests and the introduction of breast and ovarian cancer susceptibility panels raises the question of whether test criteria should be expanded or whether the general population should be screened. Enlarging the test population has serious implications given that the genes are incompletely penetrant and some women opt to have their breasts and ovaries removed rather than pursue intensified surveillance. "The case will heighten awareness of the disease and more patients will seek counseling," Dr. Klein says, "but I don't necessarily believe that the criteria for testing will change without additional evidence indicating that the benefits of screening larger numbers of patients exceed the harms of doing so." Dr. Caplan doesn't see the need for screening without finding out more information, "particularly those factors involving environment and lifestyle." Dr. Tsongalis warns, "Just because testing is available doesn't mean we should be doing it." And Dr. Arun does not think the criteria for testing should change, particularly in the absence of more data. "At the end of the day," she says, "the question is, 'Are the results going to help the patient?'"

Others, like Dr. King, believe expanded *BRCA* testing will help patients because family history is not a reliable indicator of risk, especially when family size is small or when a mutation is inherited through the paternal line. Dr. King estimates that there are 1 million women who have *BRCA* mutations of whom half have no family history. She advocates a broad screening approach because test results are highly actionable: "We know from a very large number of excellent retrospective cohort studies that women in their late 30s and early 40s and who carry a damaging mutation in one of those genes and choose to remove their ovaries and fallopian tubes at that time not only reduce the risk of ovarian cancer to virtually zero, but also reduce their breast cancer risk by half, even with hormone replacement."

Dr. Ostrer is of a similar mind, saying: "There should be *BRCA* population screening, particularly for the Ashkenazi Jewish population, regardless of family history. The criteria for testing should be expanded." With medical centers now able to offer *BRCA* testing, Dr. Ostrer says, the decision will make it possible to do clinical research because physicians can now perform the tests, aggregate the results, and correlate them to clinical outcomes. Says Dr. Gulley, "Physicians will now be able to design clinical trials differently to improve patient care from translational research."

Dr. Tsongalis

One of the paradoxes of molecular medicine is that to know more you have to test more, and this often requires new approaches and technologies. Gene patent restrictions not only put a brake on competition-driven accessible and affordable testing but also on diagnostic innovation. Gene patents restricted biotechnology companies from developing and using new methods to detect mutations in *BRCA1* and *2* and other genes. In this regard, the Court's decision will have a significant impact on technology-driven biomedical companies. One of these, TessArae in Virginia, works with academic, government, and commercial laboratories to design genetic laboratory-developed tests using its novel multiplexed technology and unique software tools. Gene patents forced customers to leave holes in their test panels, the company says. "Our technology can help pathologists and lab directors design rapid, cost-effective tests to meet the needs of their patient populations and enhance their clinical research capabilities," says the company's CEO, Tom Richards, MD. "In light of the Supreme Court decision we look forward to being able to include all the genes and variants that our clients need."

The frustration of pathologists with the restrictions gene patents imposed goes well beyond the *BRCA* genes. Says Dr. Tsongalis, "There are many other genes such as those for the cardiomyopathies, neurological disease, and cancer that offer significant clinical utility, which were previously locked up by several private labs and that will be very useful and beneficial to bring in-house." While the impact of the Court's ruling will be felt most immediately in the area of *BRCA1* and *2* testing, Dr. Klein says, "For pathologists, the case was not really about Myriad but about gene patents. Patents have been a vexing problem for people in the field that extends well beyond *BRCA1* and *BRCA2*. Pathologists see the ruling as a victory for patients and for molecular pathology."

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